September 2018

Anticancer drug; "*Elplat®*", Folinic acid; Levofolinate [Yakult]
Approval for the Additional Indication of Small Intestine Cancer

Tokyo, Japan, September 21, 2018 - Yakult Honsha Co., Ltd. (hereafter, Yakult) (President: Takashige Negishi) announced today that it obtained approval for the additional indication of "small intestine cancer", with respect to its products, *Elplat® (50 mg, 100 mg, and 200 mg)* and *Levofolinate [Yakult] (25 mg and 100 mg)*, from the Japanese Ministry of Health, Labor and Welfare (hereafter, MHLW).

It has been determined that there are high medical needs of these products for the additional indication of small intestine cancer by the 32nd "Review Committee for Unapproved or Off-Label Use of Drugs with High Medical Needs" (hereafter, Review Committee) held on August 23, 2017. Furthermore, the 34th Review Committee held on March 23, 2018, determined that such additional indication was eligible for an "Application with Public Knowledge". On April 25, 2018, the Second Committee on New Drugs of Pharmaceutical Affairs and Food Sanitation Council subsequently concluded that the Application with Public Knowledge could be allowed for such additional indication. Accordingly, Yakult had submitted such application.

Yakult will sincerely work for promoting proper use of these products, and continuously attempt to provide cancer patients and medical staffs with new treatment options.

1. *Elplat®* and *Levofolinate [Yakult]*

Elplat® is an anticancer platinum drug, for which Yakult acquired development and commercialization rights in Japan from Debiopharm in 1997. *Elplat®* was approved for the indication for the treatment of "curatively unresectable advanced/recurrent colorectal cancer" in March 2005, and launched on the market in April of the same year. In August 2009, *Elplat®* became indicated for "postoperative adjuvant chemotherapy for colon cancer". An additional dosage and administration for "curatively unresectable advanced/recurrent colorectal cancer" was approved in September 2009, and an additional dosage and administration for "postoperative adjuvant chemotherapy for colon cancer" was approved in November 2011. Subsequently, *Elplat®* was approved for the indication for the treatment of "curatively unresectable pancreatic carcinoma" in December 2013. And furthermore, *Elplat®* was approved for the indication for "unresectable advanced or recurrent gastric cancer" in March 2015 and then "gastric cancer" in November 2015, integrating "unresectable advanced or recurrent gastric cancer" and "postoperative adjuvant chemotherapy for gastric cancer".

Levofolinate [Yakult] is a generic drug of *Isovorin®,* and was approved for the indications for "enhancement of 5-fluorouracil cytotoxic activity for gastric cancer (inoperable or recurrent) and colorectal cancer" as the combination regimens of 5-fluorouracil and levofolinate and "enhancement of 5-fluorouracil cytotoxic activity for colorectal cancer" as the continuous intravenous infusion of 5-fluorouracil and

levofolinate in March 2007, and launched on the market in July of the same year. In December 2013, *Levofolinate [Yakult]* became indicated for "enhancement of 5-fluorouracil cytotoxic activity for curatively unresectable pancreatic carcinoma" as the continuous intravenous infusion of 5-fluorouracil and levofolinate.

2. Review Committee

The Review Committee is a working group organized by the MHLW aiming to accelerate the development for drugs and indications which are not yet approved in Japan but already available in Europe and U.S. by means of evaluating medical needs as well as confirming the applicability of Application with Public Knowledge and the necessity of conducting any additional studies for marketing authorization of such drugs and indications.

3. Application with Public Knowledge

Application with Public Knowledge is a kind of marketing authorization applications for a drug commonly known to be medically and pharmaceutically effective and safe without performing clinical trials in whole or in part.